

## Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain

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Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for investigation with medicinal products (hereinafter CEIm) and the Spanish Clinical Studies Registry, introduces substantial modifications in national legislation so as to make feasible the application of Regulation (EU) No 536/2014 of the European Parliament and of the Council, of 16 April 2014 (hereinafter the Regulation), and to develop those aspects that the Regulation leaves to national legislation.

This instruction document of the Spanish Agency of Medicines and Medical Devices (hereinafter AEMPS) for conducting clinical trials in Spain provides, in the form of questions and answers, information on the practical aspects involved in the application of the new Royal Decree, highlighting the changes with respect to the previous Royal Decree. This document aims to cover those aspects of Royal Decree 1090/2015, of 4 December, that are left to be developed in instructions by the AEMPS, as well as any others requiring clarification. The document is complementary to the "collaboration memo" between the AEMPS and the CEIm that is referred to in article 18 of Royal Decree 1090/2015, of 4 December, which shall also be public. The subjects requiring greater clarification or rectification based on the experience acquired shall be reviewed in successive versions of this document, which is intended to be dynamic and therefore easily updated.

Any questions or comments regarding the application of the new Royal Decree or this document should be emailed to [aecaem@aemps.es](mailto:aecaem@aemps.es), quoting "Questions and Answers" as the reference in the subject field.

Incidents or questions related to submission of an application or communication about a clinical trial via the Portal ECM should be sent to [incidensayos@aemps.es](mailto:incidensayos@aemps.es).

Incidents, questions or suggestions related to the Spanish Clinical Studies Registry (REec) should be sent to [reec\\_incidencias@aemps.es](mailto:reec_incidencias@aemps.es).



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## 1. When does the new Royal Decree enter into force?

v.13 January 2016

Royal Decree 1090/2015 entered into force on 13<sup>th</sup> January 2016.

## 2. What applications must be submitted according to the new Royal Decree?

v.13 January 2016; updated v.3 February 2016

Royal Decree 1090/2015, of 4 December, shall apply to all applications for authorisation of a clinical trial and applications for substantial modifications or notifications related to authorised clinical trials that are ongoing or for which the summary of the results has not been submitted, as of 13 January 2016. Royal Decree 223/2004 shall only continue to be applicable to those applications submitted to the Ethics Committee for clinical investigation (CEIC) or AEMPS before this date which are pending resolution by the AEMPS and also to trials for which an application for assessment by the VHP procedure was submitted before 13 January 2016.

Applications made as of 13 January 2016 shall be submitted to a single CEIm according to the regulations given in section 6.

Substantial modifications should not be submitted to the CEIm for trials which, despite having the favourable opinion according to Royal Decree 223/2004, have not yet been granted authorisation by the AEMPS. The sponsor has the option of requesting the CEIm (previous reference Ethics Committee for clinical investigation) to render void the opinion so that he or she may resubmit the application according to the new Royal Decree, including any changes considered appropriate and submitting it simultaneously to the CEIm and the AEMPS.

The second and third transitional provisions of the new Royal Decree indicate the aspects that shall remain in force only until the Regulation is fully applicable. These may be summarised in the following points:

- Applications for authorisation of a clinical trial must always be submitted complete (i.e., part I and part II).
- The current requirement for submission via the Clinical Trials with Medicinal Products Portal (hereinafter ECM Portal) and the need for qualification as product under clinical investigation are maintained.
- The periods for validation and assessment are those indicated in the Regulation, but the assessment period shall begin from the date of entry of a valid application.
- The summary of the results must be submitted to the AEMPS and the CEIm (not only to EudraCT).



- When a sponsor, due to lack of resources and until full application of the regulation, is unable to make notifications of unexpected serious adverse reactions via the Eudravigilance-CTM, such reactions may be notified to the AEMPS via the fax number +34 918225076 (see also sections 0 and 9).

### 3. Are there different rules for a low-intervention clinical trial?

v. 10 November 2016; updated v. 18 April 2017

The authorization process for a low-intervention clinical trial is the same and takes place in the same maximum periods as any other trial. However, the trial documentation and insurance are simpler (see Annex I. Trial documentation and identification of documents when loaded into the ECM Portal). In addition, monitoring, content of the master file and traceability of the investigational medicinal products may be simplified and, depending on the trial characteristics, may be similar to those in routine clinical practice.

When the sponsor requests qualification of a low-intervention study, the sponsor must indicate the request for qualification of the low-intervention clinical trial in the remarks section of the cover letter (section 2), and provide suitable justification for this qualification, indicating, when appropriate, the additional trial procedures to those that would have been performed on the participants in the context of routine clinical practice. In the decision issued by the AEMPS it will be stated whether the qualification was accepted or not, and, where appropriate, the reasons for nonacceptance.

### 4. ¿Which CEIm can perform assessment of a clinical trial?

v.13 January 2016; updated v.3 February 2016 and v.9 May 2016; updated v. 22 February 2018

*The sponsor could select the CEIm, by mutual agreement with said Committee, among the Committees included in the list that can be consulted at <https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/listado-comites-investigacion-clinica.pdf>*

*Contact data for such CEIm can be consulted at the following web:*

*<https://www.aemps.gob.es/en/investigacionClinica/medicamentos/ensayosClinicos.htm> in the “Directorio de los CEIm acreditados en España” available by clicking in “Información relativa a los Comités de Ética de la Investigación con medicamentos” (information related to Ethics Committees for Investigation with medicinal products).*

*In cases where the Ethics Committee for Clinical Investigation responsible for the clinical trial assessment is not within the above referred list, the sponsor should select another Committee from such list, by common agreement with it and request a change of the Committee according to what is indicated in section 10.*

.In the case of clinical trials authorised according to Royal Decree 223/2004, regarding applications submitted as of 13 January 2016, it shall be considered that the reference CEI that performed the initial assessment shall be the sole committee in charge of assessment



of the trial, with regard to general and local aspects in accordance with the indications contained in Royal Decree 1090/2015 and the collaboration memo.

*The change of Committee should have been done before the submission of any application or notification to the AEMPS or CEIm at the latest.*

## **5. What type of Ethics Committee for investigation can assess an observational study with medicinal products (non-interventional study) or a clinical study with medical devices?**

v. 9 May 2016; updated v. 22 February 2018

Observational studies with medicinal products and clinical investigations or observational studies with medical devices may be assessed by any of the *Committees included in the list that can be consulted at*

<https://www.aemps.gob.es/investigacionClinica/medicamentos/docs/listado-comites-investigacion-clinica.pdf>.

*When a change of the Committee responsible for the assessment of a non-interventional study or a clinical investigation with medical devices were needed, the new CEIm proposed by the sponsor has had to previously agree on taking over the study assessment. For that purpose, the sponsor must have provided the CEIm with a complete version of the study documents.*

## **6. Submission of applications and communications of a clinical trial**

v.13 January 2016; updated v. 9 May 2016, v. 10 November 2016 and v. 18 April 2017; updated in v. 8 May 2017

In the future, all applications shall be submitted via the portal mentioned in article 80 of the Regulation. Until this is operational, all applications and communications related to a clinical trial must be sent to the AEMPS and to the CEIm that has accepted assessment of the trial and shall be submitted via the ECM Portal (<https://ecm.aemps.es/ecm/paginaPresentacion.do>).

Applications must be sent only once and only via the ECM Portal.

The applicant shall be the recipient of all communications from the AEMPS on part I and from the CEIm on part II. The applicant for the CEIm may be different from the applicant for the AEMPS.

The application for authorisation of a clinical trial must be submitted with an electronic signature. In those cases where the applicant does not have an electronic signature, the date of receipt of the applications will be the date of submission in the registry of AEMPS/CEIm of the proof of electronic submission and the cover letter with his/her handwritten signature.



You can find information about digital signature certificates valid for submission of applications via the ECM Portal at the web address: <https://sede.aemps.gob.es/certDig/home.htm>

Applications must be submitted simultaneously to the AEMPS and the CEIm. Given that the ECM Portal does not currently allow this, submission must be consecutive, first to the CEIm and immediately afterwards to the AEMPS. Until the ECM Portal allows submission of documentation in a single step, the date of entry for purposes of processing of the procedure shall be considered as the date of the application that was last submitted.

In order to identify the date of entry for processing purposes and also to identify the cases in which Royal Decree 223/2004 shall continue to be applicable, the sponsor should indicate the date on which the application was sent to CEIm in the free text table of the cover letter.

All applications may be submitted at any time of the month and the date of entry shall be the date on which they were submitted.

Applications must be complete from the date of submission. No submission of additional documentation which has not been requested by the AEMPS or the CEIm shall be accepted after that date. In the event that the documentation is received later than the validation date, the evaluation schedule will be delayed<sup>(1)</sup>.

With the new Royal Decree it is foreseen that additional information may be requested both in initial applications and in substantial modifications, and both on part I and on part II. This represents a change with respect to the previous situation for which the information systems are still not adapted. Therefore, **submission of a reply to a request for information on part I in an initial application and all replies to a request for information on a substantial modification shall be sent to the CEIm** by email until it is indicated that their submission is feasible via the ECM Portal.

**The response to a condition in the authorisation** of a clinical trial or a substantial modification must be submitted to the AEMPS via the ECM Portal using "C. Response to a condition in the authorisation (of an initial application or a SM) or response to a request for information (e.g. safety)".

When the condition refers to aspects of the trial documentation received by the CEIm, it will be sent a copy of the response via the ECM Portal as a report on the progress of the trial.

**The annual safety report** will be reported to the AEMPS via the ECM Portal using "E. iv) Annual Safety Report (DSUR)" as follows:

- When a DSUR refers to a medicinal product with the qualification as an investigational medicinal product (IMP)<sup>2</sup>, a single application may be submitted simultaneously for all trials related to this IMP. To do so, the XML of the initial application form of all the

<sup>1</sup> The instructions on who to report trial dates are given in section 41.

<sup>2</sup> Medicinal products not authorised in any country of the European Economic Area containing an active substance or combination of active substances not authorised in Spain require qualification as an IMP.





clinical trials to which the DSUR refers should be loaded, clicking the button "Add Trial" and answering in all cases question "3. Does the application refer to a medicinal product with the qualification as an investigational medicinal product (IMP)?" with a "Yes" and indicating the corresponding IMP number which should have the format "yy-yyy".

- When the clinical trial is linked to more than one IMP, the DSUR corresponding to each IMP should be submitted in a separate application in the way indicated in the previous section.
- When a DSUR linked to various clinical trials refers to medicinal products without the qualification as IMPs, an application should be submitted for each trial.

**The DSUR shall be sent to the CEIm via the ECM Portal as a progress report on the trial.**

Modifications should not be sent to the AEMPS or the CEIm unless they are substantial.

Updates to the Investigator's Brochure that do not imply a substantial modification shall only be submitted as an annex to the annual safety report.

Changes in the sponsor, applicant or legal representative contact information and changes of applicant must be reported using H.- Cambio en los datos de contacto (Change in contact information). In this case, the XML and pdf formats of the updated application form must be sent as attached documents.

The way in which ***the dates of the trial are reported*** is indicated in section 41.

***The summary of results*** of the trial should be sent to the AEMPS and the CEIm no later than one year after the date of the end of the trial globally.

Submission should be made via the ECM Portal, selecting "Authorised CT" and using the function "E. Trial report (iii) Final report of results".

The summary of results should preferably follow the European format required for EudraCT and at least the Spanish version should be submitted, while it is recommended to also submit an English version. You can consult a multimedia tutorial on how to provide the results in EudraCT at <https://eudract.ema.europa.eu/whatsnew.html> (*it is recommended to read the overview on this web page before downloading and viewing the tutorials*).

## **7. How should early termination of a CT be reported when follow-up of the subjects after the termination date is anticipated?**

v. 18 April 2017

In cases where the sponsor decides to terminate a clinical trial early, it shall be indicated in the **end of trial notification** that it is an early termination and the appropriate sections shall be completed (see also section 41).

The reasons for early termination must be included in Spanish in section D.2.2.1 of the end of trial form to be published in the REec. **In the remarks section of the cover letter**



**(section 2)**, the action plan shall be indicated and whether or not it is planned to carry out additional follow-up of the subjects in the trial and its characteristics.

In those cases in which follow-up is considered necessary, the date of the end of trial shall continue to be considered the initial date on which the sponsor reported early termination of the trial. It is not required to report the date of the end of the follow-up period.

A summary of the results of the trial should be submitted within a year after the date of early termination. The results of the follow-up period should be considered part of the results of the trial, but they may be submitted at a later date as a supplementary results report.

## **8. Should suspected unexpected serious adverse reactions be reported to the CEIm?**

v.3 February 2016; updated v. 10 November 2016

No. Suspected unexpected serious adverse reactions should be reported to the AEMPS but not to the CEIm. In all cases, whether the adverse reaction occurred in Spain or in another country, notification should be made only via the Eudravigilance-CTM.

Until full application of the Regulation, when a sponsor, due to lack of resources, is unable to be a user of the Eudravigilance-CTM, he or she may report suspected unexpected serious adverse reactions to the AEMPS only through the FAX number +34 918 225 076.

The narrative of the cases may be written in English or Spanish. In the latter case it should preferably be accompanied by a summary in English.

*It is not necessary to send 6-monthly reports on unexpected serious adverse reactions.*

## **9. How should suspected unexpected serious adverse reactions and other necessary communications related to the trial be reported to the Autonomous Communities (hereinafter CCAA)?**

v.3 February 2016; v. 18 April 2017; updated in v. 8 May 2017

The documentation on safety aspects that should be sent to the health authorities of the Autonomous Communities and where it should be sent are indicated in **Annex II**.

## **10. Steps to be followed when a change is necessary in the evaluating CEIm of an authorised clinical trial:**

v.10 November 2016

When a change is necessary in the evaluating CEIm of a clinical trial:

1. The new CEIm (CREC adhered to the collaboration memo) proposed by the sponsor must have previously accepted to take over evaluation of the trial.



2. Before sending a request or communication to the new CEIm (e.g. substantial modification, DSUR submission, etc.), the CEIm must be changed in both the AEMPS and SIC-CEIC computer system. This should be done as follows:

a) Request a change in the CEIm from the AEMPS via the ECM Portal using the option "E i) Ad Hoc Reports or initial notification of urgent safety measures already taken", indicating in the remarks section of the cover letter that a change in CEIm is requested and the justification for the change, providing as attached documents the XML and PDF of the updated application form where the new CEIm is listed. A separate request should be submitted for each trial.

b) Request the change in the CEIm by sending an email to which is attached the acknowledgement of receipt of having sent the Ad hoc report to [Incidentsayos@aemps.es](mailto:Incidentsayos@aemps.es) so that the change takes place in the SIC-CEIC computer system.

3. The request may be made when the applicant has received a message from [Incidentsayos@aemps.es](mailto:Incidentsayos@aemps.es) confirming that the new CEIm has been registered in the SIC-CEIC system.

## 11. Which documents should be submitted when applying for authorisation of a clinical trial?

v.13 January 2016; updated v. 9 May 2016, v. 10 November 2016 and v. 18 April 2017

The trial documents are essentially the same as the ones currently used, but they have been classified into part I and part II. To facilitate validation and speed up processing, it is necessary that the names of the electronic documents submitted should clearly indicate their content and, if appropriate, the version date. The type of document should be correctly identified when the documents are loaded into the ECM Portal, so that the application can be considered valid (see Annex I. Trial documentation and identification of documents when loaded into the ECM Portal).

When the sponsor considers that the trial is a low-intervention trial, this should be indicated in the comments section of the cover letter that is completed in the ECM Portal and a suitable justification for that should be provided (Annex I Trial documentation and identification of documents when loaded into the ECM Portal).

The documents on suitability of the investigator and suitability of the facilities must conform to the model forms given in Annexes III and IV.

Proof of insurance cover or financial guarantee documents are included in Annexes V to VII.



## 12. What information should be provided to the potential participant in the clinical trial before obtaining informed consent?

v. 10 November 2016, updated v. 18 April 2017; *updated v. 22 February 2018*

In Annex *VIIIA*, a guideline is provided for correct preparation of a model of information sheet for the participant in a clinical trial and the informed consent document. *The paragraphs to be included in the informed consent for the collection and use of biological samples in clinical trials are indicated in annex VIIIB.*

## 13. How should authorisation for a substantial modification of a clinical trial be applied for?

v.3 February 2016; updated v.9 May 2016 and v. 18 April 2017; *updated v. 22 February 2018*

*In the remarks section of the cover letter (section 2), it shall be indicated if the modification refers only to part I, only to part II, or to both parts.*

*Modifications which only affect part II should only be sent to the CEIm and those which affect manufacture of the medicinal products or compliance with good manufacturing practice, only to the AEMPS.*

Given that a single substantial modification can refer to many changes of different importance within the authorised clinical trial, it is very important with regard to its assessment that changes are shown in a simple and summarised manner to the assessor.

The structure of the current section F of the application form (which generates the table with the previous text, the current text and its justification), as well as the use that is made of it, does not facilitate a rapid assessment of its content. For this reason, sponsors are requested to submit an additional document called «Summary and justification of changes».

The «Summary and justification of changes» document should be a summary of the changes introduced and the reasons for these in no more than 1,200 words that allows the assessor to access this information in a summarised manner in order to be able to make decisions. Therefore, the changes that are made should be adequately explained in this document, and not be a mere reference to the sections of the document that change, and the changes should be accompanied by a clear explanation or justification of the reasons for them and an assessment of the consequences of the changes for the trial participants and for the robustness and reliability of the trial results. This summary is complemented with the corresponding documents showing the old and new text and their justification or the table of changes.

When the information required in «Summary and justification of changes» is included in another document, this shall be indicated in the cover letter.

It is usual to include merely the change itself as the justification of a modification (e.g., in the justification of a modification of a selection criterion to specify «change in selection criteria»). This justification is not considered acceptable, and the reasons why the change



was made should be briefly stated. In the case of an update of different points of the investigator's brochure, reference should be made to what is relevant in the information that is updated [e.g. The results of 4 new clinical trial are added and the evaluation of all adverse events shows an increase (4% vs. 2%) in the number of cancers in the experimental versus the placebo group]. It must be emphasised this document should not be the «table of changes» in section F of the application form of a relevant modification, or in a separate document where a comprehensive list of »previous text versus new text« in the different sections or documents listing each change indicated in the Summary of Changes, or the document changed with track changes activated, which does not replace them.

Applications not including the “Summary and justification of changes” document that clearly explains the changes and reasons for the modification and the consequences of the modification, or applications that are lacking modified documents with change tracking and justification for the changes, or failing this, a table of changes, shall not be accepted as valid for processing.

The authorisation and opinion of the CEIm regarding part II shall refer only to the changes specified in the table of changes and in the modified documents with change tracking and justification of the changes that were explained in the “Summary and justification of changes” document. The sponsor is responsible for all changes specified in the summary and justification of changes that correspond to the changes included in the table of changes and in the modified documents with change tracking.

When a substantial modification is to affect various clinical trials, it is important to submit the application simultaneously for all the trials, identifying in the cover letter the clinical trials that are to be affected. This is of special interest in modifications that refer to a change in the manufacture or in the investigator's brochure of the medicinal product.

When a substantial modification refers to previously authorised changes for another clinical trial or is to document changes already adopted as previously reported urgent safety measures, this should be indicated in the cover letter.

The documents that should be submitted with a substantial modification are listed in Annex I.

See also sections 30 to 36.

## **14. AEMPS Web forms**

v.3 February 2016

The Agency shall shortly update the legal references in the ECM Portal and web page in order to adapt them to the requirements in Royal Decree 1090/2015. Meanwhile, the cover letter and forms in the current ECM Portal and web page shall be acceptable.

## **15. What should the financial budget include?**

v.3 February 2016; updated v.9 May 2016



A single financial budget should be submitted to the CEIm per trial. This should include all aspects of the contract of all participating sites. No additional amounts to those foreseen in the financial budget submitted to the CEIm may be required by the sites, unless they correspond to fees published by the competent national or autonomous community health authority in their respective official journals.

A single document may be submitted, the single financial budget of the trial, which includes variable amounts in some items whenever necessary (e.g., indirect costs applicable to the site, costs of additional tests, administrative costs of the site, etc.). Alternatively, the set of financial budgets of each of the participating sites may be submitted.

In any event, the single financial budget per trial must contain the following information:

- Costs of additional tests and cost per visit and recruited patient, with the commitment of the sponsor that the amount to be paid covers the expenses generated by the study in each site, specifying that these amounts may vary depending on the site.
- A brief text indicating that the specific amounts and other items (indirect costs and administrative costs) shall be specified in the contract of each site.
- A note indicating that the sponsor agrees to provide the investigational medicinal products at no cost and ensure that the participation of a subject in the trial shall involve no additional cost other than that which the subject would have had to incur in the context of routine clinical practice, or otherwise, justification for the additional cost.
- Planned compensations for the participants, both the nature and amount of the compensation as well as the procedure to be followed by the sponsor to deliver the foreseen compensations, this being an especially important aspect of the financial budget to be reviewed by the CEIm.

The CEIm, if it is considered necessary for the ethical assessment of the study, may request the information it considers relevant regarding the individual financial agreements for each site.

Assessment by the CEIm is considered necessary only for those modifications that imply changes in the compensations for the participants and the investigators submitted in the initial financial budget.

The AEMPS is evaluating the possibility of including a model financial budget for the CEIm in future editions of these instructions.

## 16. Which contract model should be used?

v.3 February 2016

A **single contract model** is still not available, so the currently available models should continue to be used.



## **17. What is the minimum documentation to start contract negotiation with a research site?**

v. 10 November 2016; updated v. 18 April 2017

The agreement reached on 6 October 2016 between the AEMPS and representatives of the autonomous communities involved in aspects of clinical trial management on the minimum documentation necessary for requesting management of the contract to conduct clinical trials between the sponsor and the research sites and for requesting the document on the suitability of the facilities is included in Annex IX.

## **18. Contact persons to obtain information about the requirements for managing a contract with a research site**

v. 18 April 2017; updated in v. 8 May 2017

The contact points where the sponsor can obtain information about the requirements for managing a contract with a research site are indicated in Annex X.

## **19. When can a clinical trial be started in Spain?**

v.13 January 2016

Clinical trials with medicinal products shall be subject to prior authorisation by the AEMPS after a scientific and ethical assessment of parts I and II.

Furthermore, in the case of a clinical trial with a medicinal product that includes a genetically modified organism, the sponsor shall be required to have the relevant authorisation as provided by Act 9/2003, of 25 April, on the legal regime of the confined use, voluntary release and placing on the market of genetically modified organisms (see section 25).

To be able to start a clinical trial in a participating site, the sponsor must have the favourable opinion for conducting the clinical trial at that site issued by the CEIm, the decision for authorisation from the AEMPS, and the contract signed with the site management. In addition, the sponsor must have activated the site for the trial in the Spanish Clinical Studies Registry (hereinafter REec).

If the sponsor had technical problems to activate the site in the REec, he or she may start the trial in the site after having reported the problem to [incidensayos@aemps.es](mailto:incidensayos@aemps.es).

With the aim of ensuring that the information in the REec is updated with regard to the participating sites and is useful for the patients, in substantial modifications involving the addition of a site the sponsor must send to the AEMPS, once the substantial modification has been authorised, the notification of site extension using option D i) of the ECM Portal for an authorised trial (see also section 35).



## 20. Should agreement of the management of the participating sites be submitted to obtain authorisation for the trial?

v.13 January 2016; updated v.3 February 2016

No. There should be an agreement between the site and the sponsor for the conduct of a clinical trial which is expressed in the contract. Only in clinical trials in which the sponsor is an investigator who belongs to the site and signing of the contract is not required shall express agreement of the management of the participating site be required. However, this document is only for the sponsor.

The agreement of the site management should no longer be notified to the AEMPS in the case of clinical trials authorised before 13 January 2016. In these cases, activation of the site in the REec shall be sufficient.

## 21. What fee is to be paid for the assessment of a clinical trial?

v.13 January 2016; updated v.3 February 2016 and v. 10 November 2016

The Regulation provides for a single fee payment per country but this is still not in force. Therefore, the fees to be paid to the AEMPS and to the CEIm shall be those established as up to now, and they should continue to be paid separately. Current fees for the AEMPS are specified in article 123, Group V of Legislative Royal Decree 1/2015, of 24 July, approving the Consolidated Text of Law on Guarantees and Rational Use of Medicinal Products and Medical Devices, and may be paid electronically at <https://sede.aemps.gob.es/home.htm>.

On the other hand, the exemption of current fees is that provided in article 121 section 3 of the previously mentioned Legislative Royal Decree, and it is only applicable to clinical trials investigating advanced therapy medicinal products.

See section **¡Error! No se encuentra el origen de la referencia.** on the options for reuse of a fee previously paid to the AEMPS.

The AEMPS shall inform in a timely manner of any change.

## 22. What has changed with respect to the procedure for authorisation of a clinical trial?

v.13 January 2016; updated v.9 May 2016

A single CEIm shall evaluate the trial. This CEIm shall be the one who reports to the sponsor if part II of the application is valid and the opinion on part II.

The AEMPS shall be the one who reports to the sponsor if part I of the application is valid and the schedule for assessment. The AEMPS shall also report the result of the assessment of part I, which shall reflect the assessment of both the AEMPS and the CEIm integrated into a single position. However, the sponsor must send his or her response to a



request for information on part I to both the AEMPS and the CEIm (see section 6 on how this information should be sent to the CEIm).

The AEMPS shall also issue the decision on the trial, which may be expressed as authorisation of the clinical trial, authorisation subject to conditions, or refusal of authorisation. For the decision on the trial to be authorisation or authorisation subject to conditions, this must be the conclusion on part I and also be the opinion of the CEIm on part II.

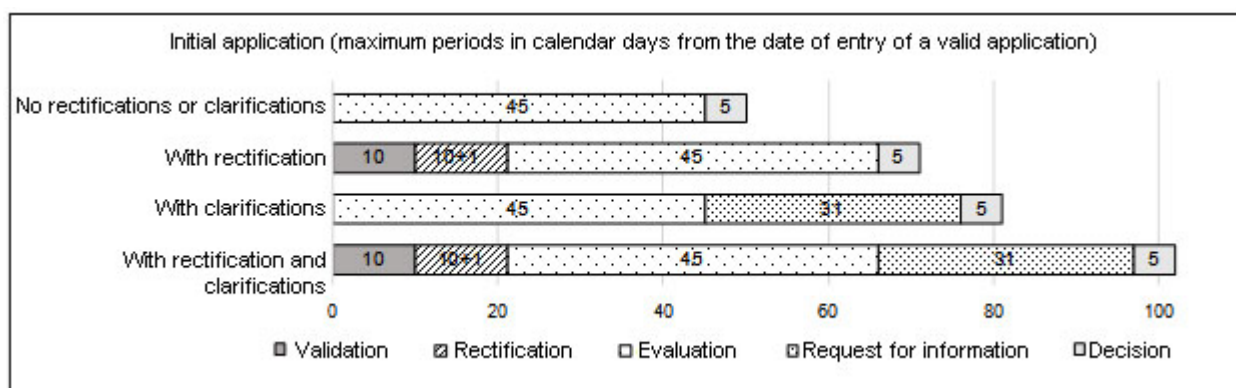
The responsibilities of the AEMPS and the CEIm with regard to the trial and the exchange of information between both bodies are set out in the collaboration memo that shall be published on the web page of the AEMPS.

Temporarily, until a common information system for the AEMPS and the CEIm is available, the sponsor must send the opinion of the CEIm to the AEMPS as soon as it is obtained, both in the case of an initial application and that of a substantial modification affecting parts I and II. Authorisation of the trial shall always be subsequent to receipt of this document.

### 23. What is the schedule followed by an application for authorisation of a clinical trial?

v.13 January 2016; updated v.3 February 2016 and v.9 May 2016

The process followed by an application from the date of entry is summarised in the following figure. In section 6 an explanation is given of what shall be considered the date of entry in the case of non simultaneous applications to the AEMPS and the CEIm, and in the case of sending an application without an electronic signature.



The CEIm shall validate part II and the AEMPS shall validate part I in a maximum period of 10 calendar days. If rectification of the application is required, the sponsor shall have 10 calendar days to submit the requested information<sup>(3)</sup> and the AEMPS (part I) and the

<sup>3</sup>In the case of non-commercial clinical trials, the maximum period for the sponsor to reply to a request for rectification of an application shall be 30 calendar days.



CEIm (part II) shall have 5 calendar days to notify the sponsor if the application is valid or not.

If part I or part II are not considered valid, the complete application shall not be considered valid.

If the sponsor fails to respond to a request for rectification of the application with regard to part I or part II within the requested period, the sponsor shall be considered to have withdrawn the complete trial application.

The maximum period for assessment shall be 45 calendar days as from the valid application date.

The valid application date is the next calendar day after the last effective entry date of an application that contains all the necessary documents for the AEMPS and the CEIm, taking into account that the entry date in the case of an application without an electronic signature shall be the entry date of the signed proof of electronic submission.

If there is a request for rectification, this date shall be the next calendar day after the date of the response of the sponsor to the request for rectification by the AEMPS or the CEIm. The last date if the response is with regard to part I and to part II.

However, it is currently not feasible for the AEMPS to know whether the CEIm has requested a rectification with regard to part II. Therefore, on a transitional basis, the period for assessment of part II shall start from the day after the date on which the response to said request for rectification was sent.

Both for part I and for part II, supplementary information may be requested once only, in this case the above period being extended by 31 calendar days (12 days for the sponsor to respond and 19 days to assess the response).

In the event of the sponsor failing to respond to a request for supplementary information during the assessment with regard to part I or part II within the requested period, the sponsor shall be considered to have withdrawn from the complete trial application.

If the sponsor decides to withdraw from part I or part II, the withdrawal shall apply to the complete trial application and the sponsor shall receive a decision notifying that said withdrawal has been accepted.

The AEMPS shall send the decision on the application to the sponsor and the CEIm within 5 calendar days of the date on which the assessment period for part I has expired<sup>(4)</sup> and the sponsor has sent to the AEMPS the opinion of the CEIm on part II. When the conclusion on part I is that the trial is authorised or authorised subject to conditions, the conclusions on part I shall be notified to the sponsor in the decision on authorisation of the trial. Only in the case that the conclusion of part I is to refuse authorisation of the trial shall the reasons be notified to the sponsor 5 days before receiving the decision.

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<sup>4</sup> In the event of supplementary information on part I but not on part II being requested, the assessment period for part I may be extended up to 31 calendar days with respect to the assessment period for part II.



The trial shall be considered to be authorised if the applicant indicated by the sponsor has not received the decision on authorisation within 5 calendar days of sending the opinion of the CEIm on part II to the AEMPS and the deadline for receipt of the conclusions on part I (whichever is later).

As an exception to the above paragraph, written authorisation shall be required in the following cases:

- When the clinical trial refers to a medicinal product that requires or has the qualification as a “producto en fase de investigación clínica or PEI” (product under clinical investigation), to an advanced therapy medicinal product, or to a medicinal product containing a genetically modified organism.
- When the AEMPS has notified the sponsor of a request for clarifications on part I within 45 days from the valid application date or the opinion of the CEIm is unfavourable.

## **24. Is the application to be considered refused in the case of clinical trials requiring a written decision, if the AEMPS has not sent the decision on authorisation within the stipulated period of 5 days?**

v.3 February 2016

The application shall not be refused in the case of clinical trials requiring a written decision if, within 5 days of having received the favourable opinion on part II and once the deadline for notification of the conclusions on part I has expired, the sponsor has not received the authorisation. The AEMPS shall make a decision in all these cases.

## **25. How should authorisation be applied for, according to Act 9/2003, of 25 April<sup>(5)</sup>, in the case of clinical trials with medicinal products containing a genetically modified organism?**

v.13 January 2016; updated v. 10 November 2016; *updated 22 February 2018*

You can obtain information regarding this on the web page of the Ministry of Agriculture, Food and Environment ([http://www.mapama.gob.es/es/calidad-y-evaluacion-ambiental/temas/biotecnologia/guiaensayosclnicosmayo2017\\_tcm30-381542.pdf](http://www.mapama.gob.es/es/calidad-y-evaluacion-ambiental/temas/biotecnologia/guiaensayosclnicosmayo2017_tcm30-381542.pdf))

## **26. Which Royal Decree should be applied to the contracts of clinical trials that are currently being processed for clinical trials whose authorisation shall be in accordance with Royal Decree 223/2004?**

v.3 February 2016

Taking into account that Royal Decree 1090/2015, of 4 December, shall be applicable to these trials once they are authorised, it is acceptable for the contract to be completed making reference to the new Royal Decree.

<sup>5</sup>Act 9/2003, of 25 April, on the legal regime of the confined use, voluntary release and placing on the market of genetically modified organisms.



## **27. What happens if the sponsor withdraws from one of the parts of the trial or fails to respond to a request for information?**

v.3 February 2016

Any withdrawal of the application before the AEMPS or the CEIm implies withdrawal of the complete trial application. This is also applicable when the sponsor fails to respond to a request for information during validation of the application or a request for supplementary information during assessment by the AEMPS or the CEIm. During validation, the sponsor shall be informed of the schedule for assessment and be provided with a contact point for any questions.

## **28. Can the application for authorisation of a clinical trial be resubmitted after withdrawal or refusal of a previous application?**

v.13 January 2016; updated v. 10 November 2016

Yes. In this case, the sponsor must maintain the same EudraCT number for the clinical trial and the same CEIm as in the previous application. In section A.6 of the application form, the appropriate letter for the resubmission number of the application should be indicated, A for the first, B for the second, etc.

When the previous application was not considered valid or if the previous application was withdrawn during the validation phase, the sponsor may reuse the fee previously paid to the AEMPS, provided it is the same as that corresponding to resubmission of the application, without having to pay it again.

The sponsor should indicate in the free text space of the cover letter that is completed in the Portal ECM what changes have been made relative to the previous application and must only attach the new versions of the documents that have changed. In this case, the document should include a section summarising all the changes in the document, or otherwise this summary of changes should be provided in a separate document. The application form should not be sent as an attached document. See also Annex I.

## **29. Is it required to send an annual report on the progress of the trial?**

v. 3 February 2016; and v. 05 April 2017 and v. 18 April 2017 updated in v. 8 May 2017

*Yes, this is required. The annual report has the purpose of facilitating the tasks of follow-up of the trial as specified in Section 4.10 of the ICH Good Clinical Practice guidelines and should conform to the format and content indicated in Annex XI.*

*The annual report should be submitted annually from the date of trial **start** in Spain and until the date of the end of the trial in Spain. The data on the number of participants in the trial shall be cumulative and annual data on serious breaches, withdrawals and discontinuations and corrective measures taken shall be indicated.*

***The annual report shall be submitted on the appropriate date, and if it is the first report, it shall include cumulative data from the start of the trial in Spain.***

It shall be submitted to the AEMPS via the Portal ECM using the option “E.- ii) Informe sobre la marcha del ensayo (E ii) Report on trial progress)” in “Ensayo Clínico autorizado (Authorised CT)” and to the CEIm by email.

### 30. What is considered a substantial modification of the trial?

v.13 January 2016

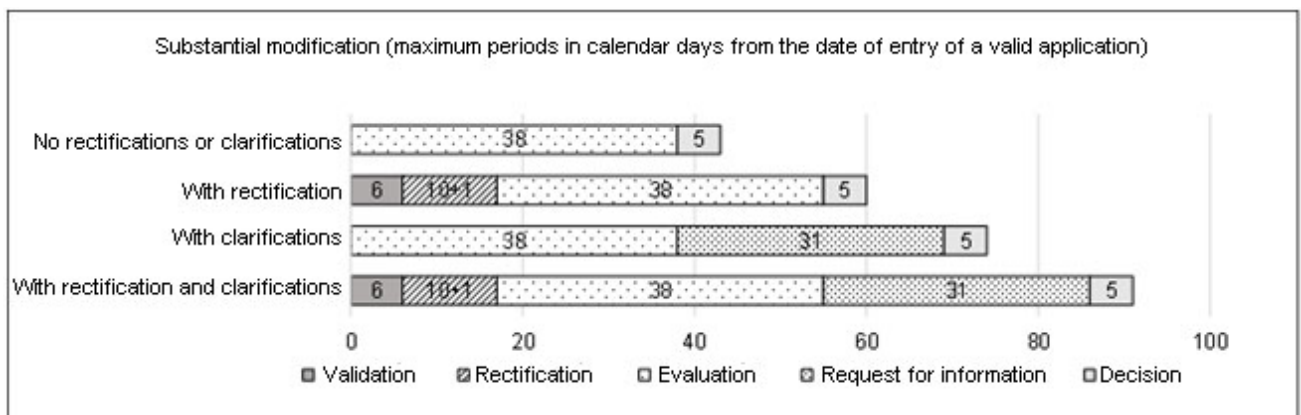
You can find examples of substantial modifications affecting part I in EudraLex, Volume 10: Chapter I of the CT-1 document, which can be consulted at [http://ec.europa.eu/health/files/eudralex/vol-10/2010\\_c82\\_01/2010\\_c82\\_01\\_es.pdf](http://ec.europa.eu/health/files/eudralex/vol-10/2010_c82_01/2010_c82_01_es.pdf).

### 31. What is the schedule followed by an application for authorisation of a substantial modification?

v.13 January 2016; updated v.9 May 2016

The process followed by an application from the date of entry is summarised in the following figure. In section 6 it is explained what shall be considered the date of entry in the case of applications to the AEMPS and the CEIm and in the event of sending an application without an electronic signature.

The same conditions as for validation of the initial application for authorisation of a clinical trial shall be applicable, but the validation period shall be 6 calendar days.



The assessment procedure for a substantial modification shall be the same as for the initial application, but the assessment period shall be 38 calendar days from the valid application date.

The reply to a request for information on part I must be submitted simultaneously to both the CEIm and the AEMPS.

In the case of a substantial modification that only affects part II, the authorisation shall be considered approved or refused on the date on which the CEIm informs the sponsor of its opinion with the conclusions on part II of the assessment report.



Substantial modifications implying changes in part I and part II shall be considered authorised if the applicant indicated by the sponsor has not received the decision on authorisation within 5 calendar days of the notification to the AEMPS of the favourable opinion of the CEIm on part II, once the assessment period for part I has ended (whichever is later).

Substantial modifications that only imply changes in part I shall be considered authorised if the applicant indicated by the sponsor has not received the decision on authorisation within 5 calendar days of the assessment period end date.

Notwithstanding what is indicated in the above paragraph, written authorisation shall be required in the following cases:

- When the modification refers to changes in the manufacture of any of the medicinal products included in the trial that requires or has the qualification as “Producto en fase de investigación clínica (PEI)”, (qualification as “product under clinical investigation”), an advanced therapy medicinal product, or a medicinal product containing a genetically modified organism.
- When the AEMPS has notified the sponsor of a request for information (clarifications) on part I within 38 days from the valid application date or the opinion of the CEIm is unfavourable.

### **32. How should a substantial modification which involves changes in parts I and II be submitted to the AEMPS and the CEIm?**

v.3 February 2016; updated v. 10 November 2016

The application should be submitted via the Portal ECM and at the same time to both bodies (first to the CEIm and immediately afterwards to the AEMPS), providing the documentation specified in section **¡Error! No se encuentra el origen de la referencia..**

### **33. Is it possible to submit a substantial modification only implying changes in part II to the CEIm before the trial has been authorised by the AEMPS?**

v.3 February 2016

No, this is not possible.

### **34. Can several substantial modifications be submitted simultaneously for the same trial?**

v.3 February 2016

As a general rule, this is not acceptable. The submission of several simultaneous applications shall be acceptable when one of them affects changes only in part I and



another affects only changes in part II, which are not related to the changes in part I, and when the modification refers to taking an urgent safety measure for safety reasons.

### **35. How should substantial modifications referring to changes in part II not related to a change in part I be notified?**

v.13 January 2016

In order to simplify assessment, the sponsor is recommended to submit substantial modifications referring to a change in the principal investigator or site extension as substantial modifications only referring to part II and hence only to the CEIm.

When the modification refers to a site extension, the sponsor should send a notification of site extension to the AEMPS so that the new sites can be seen in the REec. Said notification shall include the favourable opinion of the CEIm for the modification and the XML of the substantial modification form with the sites included in the opinion. In section 19, the necessary steps are indicated for starting the trial in a site, maintaining the trial information up to date in the REec.

### **36. How should urgent safety measures including temporary halts of a clinical trial be submitted?**

v. 10 November 2016; updated v. 18 April 2017

Should there be any circumstances that might affect the safety of the subjects, the sponsor and the investigator shall take the appropriate urgent safety measures to protect the subjects against any immediate risk. The sponsor shall inform both the AEMPS and the CEIm of these circumstances and the measures taken to minimise the risks and discomforts for the participants as soon as possible. This notification should indicate the date on which the trial was halted (if it involves a partial or total halt of the trial), the justification for taking this measure, the effect of the measure (countries or sites affected when not all **of them**, recruitment halted, treatment interruption, complete halt of the trial, number of patients affected, etc.) and a report on the current status of the trial, at least in Spain.

This notification will be made via the Portal ECM as one of the following:

- "E i) Informes Ad Hoc o notificación inicial de medidas urgentes de seguridad ya adoptadas (E i) (Ad hoc report or initial notification of urgent safety measures already taken).
- "B.- Modificación sustancial" (Substantial modification)

"E i) Informes Ad Hoc o notificación inicial de medidas urgentes de seguridad ya adoptadas" (Ad hoc report or initial notification of urgent safety measures already taken) will be used for notification when these measures do not imply a substantial change affecting any of the trial documents (e.g. protocol, investigator's brochure, etc.) and when the measures taken imply substantial changes but at the time of making the notification the documents required for requesting the substantial modification are still not available.



When authorisation is requested for a "Substantial Modification" in the substantial modification form, the checkbox "E.2.5 Esta modificación se refiere a medidas de seguridad ya adoptadas (This modification refers to urgent safety measures already taken)" should be marked "yes". When the urgent safety measure also implies a temporary halt to the trial, in the modification form the checkbox "E.2.6 Esta modificación es para notificar una paralización urgente del EC" (This modification is to notify an urgent halt of a CT)" will also be marked "yes" and section E.4 will be completed. In addition, as with any other substantial modifications, the "Summary and justification of changes" document and the table of changes, or failing this, the corresponding modified documents with change tracking, shall be provided.

It is recommended to indicate in the free text box of the cover letter (carta de acompañamiento) to be filled in Portal ECM if the urgent safety measure was previously notified as an ad hoc report.

If the trial is terminated as a result of the reason that led to a temporary halt, the relevant notification of termination of a clinical trial should be made.

### **37. Particularities in the time schedules during the Christmas period**

v.13 January 2016; updated v. 10 November 2016

As currently accepted in the voluntary harmonisation process - VHP (see "key documents list" in <http://www.hma.eu/ctfg.html>) and as indicated in the functional specifications for the EU portal and database which shall be auditable,<sup>(6)</sup> between December 23 and January 7 there shall be a clock stop in all applicable time frames during that period, unless prior to the application it has been agreed with the AEMPS and the CEIm that the assessment may be performed without that clock stop.

### **38. Particularities in the case where the sponsor submits a clinical trial in which the CEIm participates in the voluntary harmonisation process (VHP)**

v.13 January 2016; updated v. 9 May 2016 and v. 18 April 2017

It is considered necessary to involve the CEIm in applications for assessment under the VHP affecting Spain, given that according to the new royal decree, assessment of part I is the joint responsibility of the AEMPS and the CEIm, as indicated in the collaboration memo. When the CEIm has participated in the VHP procedure (see «key documents list» in <http://www.hma.eu/ctfg.html>), the position indicated by the AEMPS in the VHP shall be also binding for the CEIm.

When the VHP coordinator is submitted an initial application for a clinical trial or a substantial modification regarding the protocol or the investigator's brochure for assessment, the

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<sup>6</sup> [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Other/2014/12/WC500179339.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179339.pdf)





acceptance of the relevant ethics committee in Spain (specify name) participating in the VHP assessment should be indicated in the cover letter.

For the CEIm indicated by the sponsor to participate in the VHP there are two options: the sponsor submits simultaneously part I to the VHP coordinator and the complete trial application or substantial modification via the ECM Portal to the CEIm (the same documents corresponding to part I submitted under the VHP and, if applicable, part II), or the AEMPS sends to the CEIm the corresponding documentation from the VHP application. In both cases, the AEMPS shall transmit in the VHP the overall position of Spain on part I (integrating the opinion of the CEIm), and the opinion expressed in the VHP shall be binding for both the AEMPS and the CEIm.

When an initial application for authorisation of a clinical trial or a substantial modification that has been assessed or is to be assessed under the VHP is submitted, this circumstance should be indicated in the cover letter so as to facilitate their distinction from other applications.

Once the VHP has ended, the application for authorisation sent to the AEMPS must necessarily include the opinion of the CEIm provided that it is an initial application or one that refers to a substantial modification of part I that also implies changes in part II, even though in the event that of the CEIm not participating in the VHP assessment, this shall result in a delay in the application for authorisation of the trial.

In the case of a substantial modification, it should be indicated in the cover letter if the modification affects only part I or part I and part II.

If the application for the opinion of the CEIm was not submitted in parallel with the VHP via the ECM Portal, the CEIm must receive it subsequently. This application shall include the documentation assessed and accepted for the VHP and that corresponding to part II if applicable.

In the event of the CEIm not participating in the VHP assessment, upon receipt of the application for an opinion, the maximum periods for assessment in the national schedule shall be applied, and in the event that the CEIm requires additional information on part I, this request shall be addressed to the sponsor directly by the CEIm. The sponsor shall include a copy of said reply in the application for authorisation of the trial or substantial modification to be sent to the AEMPS.

Applications for substantial modifications only affecting part I, in which the CEIm did not participate in the assessment, shall be submitted to the AEMPS once the VHP assessment has been completed and immediately after their submission to the CEIm.

The authorisation of the trial, upon receipt of the official application in the AEMPS and once the VHP has been completed, shall be within ten days, although the sponsor shall receive the notification that the application is valid according to the standard assessment schedule.



### **39. What is considered to be an auxiliary medicinal product in a clinical trial?**

v.13 January 2016

The term 'auxiliary medicinal product' is equivalent to the term 'non investigational medicinal product'. Therefore, auxiliary medicinal products are described in the guideline [http://ec.europa.eu/health/files/eudralex/vol-10/imp\\_03-2011.pdf](http://ec.europa.eu/health/files/eudralex/vol-10/imp_03-2011.pdf)

### **40. Should the sponsor of a clinical trial provide the investigational medicinal products and auxiliary medicinal products in the trial?**

v.13 January 2016

The sponsor is responsible for providing the investigational medicinal products at no cost. In clinical trials sponsored by an investigator of a site or a non-profit scientific entity, or in those where there is mutual agreement with the site management where the clinical trial is to be conducted, other means of supply may be agreed with the site, particularly when treatment of the patients in the trial, or part of it, were the one they would receive if they decided not to participate in the trial. In any case, the sponsor must ensure that participation of a subject in the clinical trial shall involve no additional cost other than that which the subject would have had to incur in the context of normal clinical practice.

### **41. Publication of the dates of trial start , of first visit of the first subject, of the end of recruitment,of the end of the trial, of reasons for early termination and of date of the final tSummary of results report in the REec**

v.13 January 2016; updated v. 10 November 2016; and v. 18 April 2017 updated in v. 8 May 2017

The sponsor must notify the AEMPS and the CEIm of the following trial dates:

#### **1. Trial start date in Spain.**

In general, the first act of selection of **potential subjects** for a clinical trial. this could be understood as the start date of the trial in the first site, that is, the date on which it is considered that the first site is ready to begin to recruit.

#### **2. Date of first visit of the first subject included in Spain.**

This should be understood as the date on which the first subject selected in Spain or his/her legally designated representative signs informed consent to participate in the trial.

#### **3. Recruitment end date in Spain.**

This is considered as the date on which subject selection in Spain is concluded.

#### **4. Trial end date in Spain and trial end globally.**



In general, the trial end date will be considered as the date of the last visit of the last patient.

**In the case of early termination of the trial, it will be considered as the end date of the trial.**

The maximum period for notification in all cases shall be 15 calendar days from the date of occurrence of the circumstance, specifying the reasons in the case of an early termination (see also section 7). The reasons for early termination must be included in Spanish in section D.2.2.1 of the end of trial form to be published in the REec.

All dates related to the trial shall be reported via the ECM Portal using the applications for an authorised clinical trial. The trial start date shall be indicated using section "A. Notification of trial start date". The date of the first patient visit and the recruitment end date in Spain and the end date globally shall be indicated in the cover letter of section "E) i) Ad Hoc Reports or initial notification of urgent safety measures already taken". The trial end date in Spain shall be notified using "F. Notification of trial end date".

In addition, the sponsor shall send a copy of the summary of results published in EudraCT to the AEMPS and the CEIm no later than one year after the date of the end of the trial.

The trial results should be sent via the ECM Portal using the section E. Trial report iii) Final report of results.

When the analysis of the results of a substudy of a clinical trial ends on a later date than the rest of the trial, it shall be necessary to submit the summary of the results to the AEMPS and the CEIm during the year following the end of the trial, without this involving a delay in submitting the results of the rest of the trial.

All the information mentioned above shall be published without delay in the REec.

It is important that the sponsor report to the AEMPS all dates and information that should be published in the REec, even if there is a delay with regard to the periods established for this communication.

## **42. Update of participating sites in a clinical trial in the REec**

v. 10 November 2016; updated v. 18 April 2017; *updated 22 February 2018*

When the AEMPS authorises a clinical trial or processes a notification of site extension, the sites accepted by the CEIm in the opinion on part II will be visible in the REec and listed as *no iniciado (not started)*.

In order to facilitate participation in the trial and follow-up of the activity of the sites participating in the trial, the person designated by the sponsor as responsible for updating the information in the REec must keep the status of the sites updated as follows:

- *No iniciado (Not started)*: the trial is authorised and the site has the favourable opinion of the CEIm to participate in the trial, but the trial has not started in the site (red).



- *Activo (Active)*: from the time the site begins to accept new subjects to participate in the trial until the last visit of the last treated subject takes place and the site is closed (green).
- *Cerrado (Closed)*: The trial has ended in that site (white).

#### **43. There shall be a record in the REec of the date of site activation. Sponsor contract in the REec**

v. 10 November 2016

The contract that is shown to request more information about the trial in the REec corresponds to the information in section: "B.5 Contact point designated by the sponsor to obtain additional information about the clinical trial" from the initial application form.

Since this is a contract of interest for investigators and potential participants in the trial, the sponsor needs to select a mailbox that is institutional if possible, where it is possible to answer in Spanish the queries made in Spanish and it is also of great interest and highly recommendable that the telephone is in Spanish.

#### **44. Person or entity designated by the sponsor as responsible for the study in the REec**

v. 10 November 2016; *updated 22 February 2018*

The person or entity designated by the sponsor as responsible for the study in the REec is responsible for updating the trial information in the REec. When submitting the application for authorisation of the trial, the applicant will indicate in the cover letter the email of the one designated by the sponsor as responsible for the REec as follows: next to the text: "Responsable de la información del estudio en REec" ( responsible for study information in the REec), "Usuario responsable en REec" (User responsible in REec) should be selected and where it is indicated "Especifique el Correo electrónico del Usuario responsable de la información en REec" (Specify the email of the user responsible for information in REec) it is very important to include an email address. This responsible person or entity will receive in the specified email a message to active his/her account in REec when the trial is published due to being authorised. If this information is not correct, the access codes will be automatically sent to the email specified in point C.1.4.6 of the initial application form: Solicitante a la AEMPS (Applicant to the AEMPS).

The responsible for the study in the REec will keep track of the information in the REec. He/she may create new users (without limit) and *assign e* them to their clinical trials *or delete them*. He/she must also add the study rationale and manage activation and *closing* of the sites.



*In case of difficulty, please, indicate which is the problem in an e-mail send to soporte\_reec@aemps.es.*

#### **45. What information can manage the responsible for the clinical trial in the REec?**

v. 10 November 2016; updated v. 18 April 2017; *updated 22 February 2018*

After entering the REec webpage with his/her user name and password, the responsible person of the clinical trial may:

- Edit the study rationale.
- Change the states of the trial sites (not started, active, and closed).
- Assign or *delete* users to their study. These users can be registered by the responsible for the study in the REec.
- A phase I clinical trial not including *paediatric* population, *will be published with reduced information in the REec.. The responsible for the study in the REec can expand publication to all the clinical data. by pressing the green button F1 “publicar datos de fase I”*. As a result, the trial will show the same amount of information as all other trials.

#### **46. How can I change the user responsible for the clinical trial in REec?**

v. 10 November 2016; *updated 22 February 2018*

The responsible for the trial in REec can create a new responsible user and *cease to be so. In order to do that, he/she has to enter in the REec with his/her access codes, open the study and press the blue button “reassignación de studios”*.

#### **47. What information is published in the REec?**

v. 10 November 2016; updated v. 5 de abril 2017; *updated 22 February 2018*

The data published in the REec are from the application form, trial dates and results provided by the sponsor via the Portal ECM. The only information that must be included directly in the REec is the trial rationale and *management of the status of the sites*.

##### Management of the status of the sites

This is done by clicking directly on the site in the study detail and modifying the value from "no iniciado (not started)" to "activo (active)" when the trial is started in the site or to "cerrado (closed)" when the trial has ended (see also section 42).

##### Rationale

The responsible for the clinical trial in the REec must include this information within 14 days of publication of the trial and it is then validated by the AEMPS. The information will be made public when it has been validated by the AEMPS.



*The rational for the CT has to met the following characteristics:*

- 1. Language should be appropriate for lay persons, avoiding as much as possible, abbreviations and signs.*
- 2. It should be in both Spanish and English.*
- 3. No more than 2000 characters.*

In case the validation is not passed due to non compliance with some of the required characteristics, this will be notified to the responsible for the study in the REec asking for an amend of such information.

#### Publication of studies

*As soon as the clinical trial is authorised, it is published in the REec. Then, , the responsible for the study in the REec will receive an e-mail with the confirmation of publication of the study.*

If the responsible for the study in the REec does not have any study assigned previously in the REec (i.e., he/she is not a registered user in the REec), he/she will receive an email at the time of publication of the clinical trial *with the user and password to do the management of his/her trial in the REec.*

If he/she is listed as a registered user in the REec, an email will be sent indicating that a new study has been published associated with his/her user name.

#### Publication of phase I studies not including the **paediatric** population

*Publication in the REec is automatic for all authorised clinical trials. However, when they are phase I and do not include the paediatric population, only reduced information of the trial is published (EudraCT No, sponsor, phase, type of study population and number of subjects, study scope, participating sites, trial dates). The responsible for the REec can expand the publication to the standard information available for all trials.*

#### Publication of the trial dates and reasons for early termination

See section 41.

#### Publication of clinical trial results summary

The **summary** report of results sent to the AEMPS (see section 6) will be automatically published in the REec as soon as it is received. The sponsor will be solely responsible for the accuracy of the data provided.

## **48. Summary of intermediate report of results and summary of the final report of results**

v. 18 April 2017; updated 22 February 2018

It can be foreseen in a clinical trial that there may be several analyses of results that are performed at different times (e.g. efficacy and safety after all patients have followed 1 year of treatment and after 3 years of treatment). In these cases, as required in Article 37.8 of



Regulation 536/2014, **a summary of** these results should be reported to the Member States. On the other hand, a publication of the analysis of intermediate results is commonly made.

When it is planned to perform intermediate results analysis in a trial, the sponsor must indicate if it is planned to make public these analyses before the final analysis of results is available. If in the authorised protocol it is planned to publish intermediate results before the end of the trial, the sponsor must send a summary of the intermediate results for their publication in the REec within one year of analysis of the intermediate data.

The summary of intermediate results **and the summary of final results** should not be a preliminary or draft analysis but contain the final data of the analysis.

#### **49. Aspects that should be taken into account by the sponsor so that data collection in the Case Report Form (CRF) complies with legislation on data protection**

v. 18 April 2017

The case report form (CRF) of a clinical trial is not a document to be included in the application for authorisation of a clinical trial and therefore should not be submitted to the AEMPS or the CEIm. The key aspects so that the sponsor can comply with current regulations are highlighted in this section.

Regulation (EU) No 536/2014 requires that the data of trial subjects be processed in accordance with EU legislation on data protection. In Spain, application legislation is the Organic Law 15/1999, of 13 December, on the protection of personal data (LOPD), resulting from the transposition of European Directive 95/46/EC, and Royal Decree 1720/2007, of 21 December, which approves the Regulation implementing the LOPD. This Royal Decree requires the application of high-level security measures in the management of health data, so that the distribution of the supports is done encoding these data or using another mechanism that guarantees that this information is not accessible or manipulated during transport.

Health-related data are considered by the LOPD to be specially protected data that warrant a stricter regimen of protection, which is a wider concept including information regarding the past, present and future physical or mental health of an individual, as well as the level of disability and genetic information of the person. For this reason, the case report form should only include a code not allowing identification of the subject. In addition, identifying data of the subjects participating in the study can not be collected: the medical history number or similar assigned by the Administration, name, surname, or initials of the subject, postal or email address, telephone number, tax identification number, digital fingerprint, DNA, a photograph, social security number, etc.<sup>7</sup>.

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<sup>7</sup> references: Farmaindustria's "codigo tipo" for personal data protection in clinical research and pharmacovigilance.



In some clinical trials in which the sponsor may require access to personal data of the subjects participating in a clinical investigation study, this situation must be justified in the protocol and specified in the informed consent of the participating subject. In this case, the sponsor is required to notify previously the creation of a file of Case Report Forms (FCRD) in the Register of the Spanish Data Protection Agency (AEPD).

## **50. How long should the master file of a trial authorised with Royal Decree 223/2004, of 6 February 2004, regulating clinical trials with medicinal products, be retained?**

v. 9 May 2016

The legislation applicable to the archiving period of the master file from the entry into force of Royal Decree 1090/2015, of 4 December, is its article 43, according to which “1. *The clinical trial master file shall comply with the provisions laid down in articles 57 and 58 of Regulation (EU) No 536/2014 of the European Parliament and of the Council, of 16 April 2014. The content must take into account the supplementary guidelines in this regard published by the European Commission. 2. The sponsor and investigator shall keep the contents of the master file in paper or digital format of each clinical trial **during at least twenty-five years after the end of the trial**, or for a longer period if this is set down in other applicable requirements, such as in the case of the study being submitted as a basis for the authorisation of a medicinal product which must comply with Annex I of Royal Decree 1345/2007, of 11 October, or an agreement between the sponsor, the investigator and the site.(...)*”.

In this regard and pursuant to the sole repealing provision of Royal Decree 1090/2015, of 4 December, Royal Decree 223/2004, of 6 February 2004, regulating clinical trials with medicinal products, and Order SCO 256/2007, of 5 February, establishing principles and detailed guidelines for good clinical practice and the requirements governing the authorisation of the manufacture or importation of investigational medicinal products for human use, **are hereby repealed, which is the reason why the five-year archiving period of the master file regulated in the previous Royal Decree can no longer remain in force.**

Regarding the principle of non-retroactivity, Royal Decree 1090/2015, of 4 December, does not have a retroactive nature, since, in accordance with article 2, paragraphs 2 and 3 of the Civil Code: “2. *Laws may only be repealed by subsequent laws. Such repeal shall have the scope expressly provided therein, and shall always extend to any provisions of the new law on the same matter which are incompatible with the previous law. Mere repeal of a law shall not entail recovery of the force and effect of any provisions repealed thereby. 3. Laws shall not have retroactive effect, unless otherwise provided therein*”.

Consequently, for clinical trials that have been authorised in the framework of Royal Decree 223/2004, of 6 February, the following should be taken into account. Irrespective of whether or not it has retroactive effect, Royal Decree 1090/2015, of 4 December, is the current





regulatory framework for clinical trials in Spain, and given that there is no transitional disposition on the archiving period of the master file, and irrespective of whether the clinical trial was approved according to Royal Decree RD 223/2004, of 6 February –as this decree has been repealed–, the archiving period of the clinical trial master file must be the twenty-five years provided for in article 43 of Royal Decree 1090/2015, of 4 December, since this is the legislation currently applicable to clinical trials.

Finally, with regard to clinical trials that have concluded under Royal Decree 223/2004, of 6 February, the archiving period of the documentation shall be that provided in aforesaid Royal Decree, i.e., five years.

## **51. When should observational studies be loaded into the REec?**

v.3 February 2016; updated v. 10 November 2016

When an update to the regulations applicable to these studies becomes available, guidelines will be provided to facilitate this task.

## **52. How should the serious breaches referred to in article 29 be reported?**

v.3 February 2016; v. 18 April 2017 updated in v. 8 May 2017

The sponsor of a clinical trial should report to the AEMPS and the CEIm a serious breach of current clinical trial legislation or of the version of the protocol authorised at the time of the breach that has occurred in Spain without delay and not later than seven calendar days from becoming aware of the breach.

For this purpose, a serious breach shall be understood to be a breach that may significantly compromise the safety and rights of the trial subjects or the reliability and robustness of the data obtained in the clinical trial.

Until submission via the Portal ECM is feasible, serious breaches should be reported to the Department of Inspection and Control of Medicinal Products of the AEMPS via the email [incumplimientosgraves@aemps.es](mailto:incumplimientosgraves@aemps.es). The report shall be made using the form and according to the instructions in section "4. NOTIFICACIÓN DE INCUMPLIMIENTOS GRAVES DE ENSAYOS CLÍNICOS (Notification of serious breaches of a clinical trial)" in <http://www.aemps.gob.es/industria/inspeccionBPC/home.htm>.

Serious breaches shall be reported to the CEIm via email.

From publication of these instructions, only deviations considered a serious breach should be reported to the AEMPS and the CEIm.

**Queries about this subject should be sent to the email [area\\_bpc\\_bpfv@aemps.es](mailto:area_bpc_bpfv@aemps.es).**



### **53. Clarification on application in Spain of Annex VI of Regulation (EU) No. 536/2014 on labelling of investigational medicinal products and auxiliary medicinal products**

v. 10 November 2016

Until the above Regulation is fully applicable, Annex 13 "Manufacture of Investigational Medicinal Products" from Good Manufacturing Practice will continue to be applicable in Spain.

### **54. In which cases shall it be required to request authorisation of compliance with good manufacturing practice by the AEMPS for the manufacture or distribution of medicinal products by the hospital pharmacy department?**

v. 23 June 2017

**54.1 This authorisation shall be required for total or partial manufacture of investigational medicinal products, as well as for some processes of dividing up and packaging, whereas the following processes shall be exempt:**

a) *Relabelling.*

b) *Repackaging, when it consists of:*

- *modification of the secondary packaging of all dosage forms.*
- *modification of the primary packaging only for solid oral dosage forms (tablets and capsules).*

*Although authorisation is not required in these cases, the application for clinical trial authorisation must be accompanied by the following documentation:*

- *Standard operating procedure (SOP) describing in detail the modifications of both the primary and secondary packaging occurring in the investigational medicinal products.*
- *In cases of modification of the primary packaging, an evaluation of the impact that this modification may have on the final quality of the product should be provided. This is to provide justification for the suitability of the new primary packaging of the investigational medicinal product and the expiry date and stability of the modified medicinal product in its new packaging.*

c) *Reconstitution. Reconstitution shall be understood as the simple process of:*

- *dissolving or dispersing the investigational medicinal product for administration of the product to the trial subject, or*



- *diluting or mixing the investigational medicinal product with some other substance used as a vehicle for the purpose of administering the product (without being repackaged in a new packaging).*

*Reconstitution is not the mixing of different components of the formulation, including the active ingredient, to produce an investigational medicinal product.*

*The investigational medicinal product has to exist previously so that a process can be defined as reconstitution.*

*The reconstitution process should be immediately before administration.*

*This process has to be defined in the clinical trial application/investigational medicinal product dossier and in the clinical trial protocol or related document available in the site.*

**54.2. When the investigational medicinal product(s) are distributed from a hospital pharmacy department to the other sites participating in the trial, authorisation of compliance with good manufacturing practice should also be requested for those sections applicable to distribution.**

## **55. Is authorisation by the AEMPS required to prepare a magistral formula intended for a clinical trial?**

v. 23 June 2017

Magistral formulas and officinal preparations are medicinal products for human use that are defined in Article 8, paragraph 1b and 1c of Royal Legislative Decree 1/2015, of 24 July, approving the consolidated text of the Law on guarantees and rational use of medicinal products and medical devices.

In the event that the investigational medicinal product meets the definition of a magistral formula or officinal preparation prepared in an authorised pharmacy department (as defined in RD 175/2001), the following shall be taken into account:

A) If the investigational medicinal products are classified magistral formulas or officinal preparations, as they are formulas known and described in the National Formulary manufactured in an authorised pharmacy department, it shall not be required to request authorisation of manufacturing from the AEMPS. In this case, the following should be done:

- Attach, along with the other trial documentation, a document with the reference to the magistral formula in the National Formulary. A copy of the relevant page of the National Formulary containing this formulation is acceptable.
- Indicate this in the cover letter filled in in the Portal ECM: in the section “Descripción de los procesos realizados por la Oficina de farmacia” (Description of processes performed by the pharmacy department)”, choose the option “Otras” (Other) and specify “Classified magistral formula”.



B) If the investigational products are unclassified magistral formulas (i.e., not described in the National Formulary), the relevant authorisation must be requested from the AEMPS. The procedure detailed in the next point of these instructions shall be followed.

In the event that this unclassified magistral formula is prepared regularly in the Pharmacy Department, this should be stated in the free text space of the cover letter and the available data on efficacy and safety of this treatment be provided.

## **56. What is the procedure for requesting authorisation of manufacturing/distribution by the hospital pharmacy department?**

v. 23 June 2017

*At the same time as submitting the application for clinical trial authorisation, the request for authorisation of manufacturing by the pharmacy department should be included providing the following documentation:*

### **1. APPLICATION FORM for authorisation of manufacturing specifying the following:**

- *Title of trial and EudraCT No.*
- *The investigational medicinal product it is desired to manufacture and its dosage form (this includes any placebo).*
- *Pharmacy department where the manufacturing process will be performed.*
- *If the investigational medicinal product will be delivered from a pharmacy department to the other participating sites.*

*The application must be signed by the SPONSOR and by the person responsible for the PHARMACY DEPARTMENT.*

### **2. PROTOCOL (or protocol summary):** *It shall include complete information about the manufacturing operations to be performed in the pharmacy department.*

### **3. DOCUMENT EQUIVALENT TO THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER QUALITY PART,** *where the following is specified:*

- *The manufacturing operations involved; types of placebo and blinding that are planned to be performed, indicating the medicinal products and pharmaceutical forms to which they refer.*
- *The manufacturing and control process, with the relevant documentation.*
- *Identification of the manufacturing site, specifying the premises, technical team and control processes.*

### **4. AGREEMENT AND ACCEPTANCE** *of the Director of the site where the manufacturing operations are to be performed. This agreement is different from the agreement of site management to conduct the clinical trial.*

### **5. SOP for distribution of investigational medicinal products** *when the pharmacy department will send the medicinal products of other trial sites.*



The annexes of this document are published separately and listed below. Amended annexes are indicated in *red*.

**Annex I. Trial documentation and identification of documents when loading these into the ECM Portal**

**Annex II. Safety related documentation that the sponsor should submit to the health authorities of the Autonomous Communities (AC).**

**Annex III. Suitability of the investigator.**

**Annex IV. Suitability of the facilities.**

**Annex V. Insurance certificate Model.**

**Annex VI. Sponsor's commitment for non-commercial clinical trials Model.**

**Annex VII. Certificate of site / organization representative for low-intervention clinical trials Model.**

**Annex VIIIA. Guideline for correct preparation of a model patient information sheet and informed consent form (PIS/ICF).**

***Annex VIIIB. Paragraphs to be included in the Informed Consent for the collection and use of biological samples in clinical trials.***

**Annex IX. Minimum documentation necessary for requesting management of the contract to conduct clinical trials between the sponsor and the research sites. Date: 6 October 2016.**

**Annex X. Contact persons for managing a contract with a research site.**

**Annex XI. Annual follow-up report of the clinical trial.**